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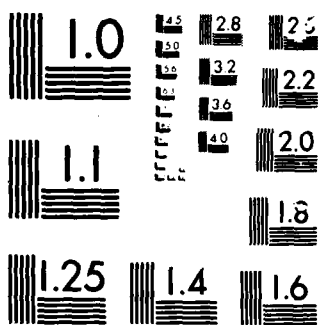
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ANNUAL REPORT AUGUST 31, 1983

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EFFECTS OF RADIATION INJURY TO THE LUNG

ANNUAL REPORT

LYN A. THET, M.D.

AUGUST 31, 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-82-C-2238

Duke University
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SUMMARY

The purpose of the work was to study the effect of WR2721, without without corticosteroids, on acute and chronic lung injury caused by a sublethal dose of ionizing radiation. The model used was that of 3000 rads unilateral radiation to the left lung of adult rats. The degree of injury and the amount of protection were to be assessed at 12 weeks, 26 weeks and 52 weeks post-radiation by quantitative ultrastructural examination and physiologic measurements.

To date, we have completed full ultrastructural morphometry on about half the animals scheduled to be studied at 12 weeks post-radiation. At this early time point, WR2721 alone does not seem to confer significant protection. However, WR2721 plus corticosteroids seemed to decrease the amount of radiation injury as evidenced by the following when compared to the group receiving radiation alone: less volume of cellular and non-cellular interstitium, less number of alveolar macrophages and interstitial cells, lesser mean thickness of the interstitium, and increased volume of intra-capillary blood.

We conclude that WR2721 and corticosteroids have the combined effect of reducing lung injury present 12 weeks after a single dose of 3000 rads. The effects of WR2721 alone were not noticeable at this early time point, but might perhaps be significant at later time points.

FORWARD

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

TABLE OF CONTENTS

1. STATEMENT OF THE PROBLEM	4
2. BACKGROUND	4
3. APPROACH TO PROBLEM	5
4. RESULTS	6
5. DISCUSSION OF RESULTS	6
6. TABLE 1. Changes in cell number and total volumes in the left lung of rats 12 weeks after unilateral irradiation.	7
7. TABLE 2. Changes in total surface area and mean arithmetic thickness in the left lung of rats 12 weeks after unilateral irradiation.	8
8. OTHER ACCOMPLISHMENTS	9
9. PROBLEMS ENCOUNTERED	10
10. FUTURE PLANS	
11. REFERENCES	11-12

STATEMENT OF THE PROBLEM

Radiation injury to the lung results in acute and chronic effects leading to morbidity and mortality (1-15). WR2721 is the most efficient radioprotective agent currently available but is less effective for the lung than for other organs, at least in terms of preventing mortality (8-10). There have been no quantitative or even qualitative morphological studies regarding the protective effect of WR2721 in the lung; to our knowledge, there have also been no studies of the protective effect or physiological functions other than on breathing frequency (4).

BACKGROUND

(1) Response of the lung to radiation injury

The lung is regarded as a moderately radio-sensitive organ with a slow renewal population of cells, that is, only a small fraction of the cells are multiplying at any one time (15). Nongenetic early damage probably occurs in the endothelial and epithelial cells, and the late effects are thought to be related to genetic damage in the endothelial and/or Type II cells (15). However, the specific details are probably very complex and are not well understood since no quantitative data on the numbers of cells and the morphological changes in different cellular and extracellular compartments is available. For example, because the absolute number of cells has not been measured, it is not clear whether the endothelial cells or the Type II epithelial cells are the main site of initial injury.

The response of the lung to injury is generally divided into 3 phases. The early changes (0-2 months) are thought to be due to the acute damaging effects of radiation causing swelling, damage and increased capillary permeability leading to an exudative reaction (16,17). Fragmentation of connective tissue may also take place (18). Intermediate changes (2 and 9 months) are thought to occur when genetically damaged cells reach mitosis, resulting in anaphase arrest or non-viable daughter cells (15). The destruction of basement membrane may also result in greater disorganization of lung tissue architecture (19). The late phase (after 9 months) is associated with the development of fibrosis (20,21).

(2) Effect of WR2721 on radiation injury to the lung

WR2721 or S-2-(3-aminopropyl amino) ethylphosphorothioic acid is the most efficient radio-protective drug now available (8,10). The proposed mechanism of protection is that the sulfhydryl groups on the compound help repair the damage caused by radiation-generated free radicals (10). The amount of protection avoided to the lung is relatively less than that conferred to other organs. In experimental studies in mice using mortality rate as an indicator, WR2721 is reported to confer a protective effect of 1.2 to 1.8 times (8). In a very recent abstract (4), breathing rate and lethality were used as an index of lung damage; the protective factor was 1.2 to 1.3 times in the early (3 to 5 months) phase, and 1.4 to 1.5 in the late (more than 7 months) phases of fibrosis. These data suggest that WR2721 offers more protection against late fibrosis than early pneumonitis in mouse lung. To our knowledge there have been no morphological and functional studies done to assess the efficacy of WR2721 in modifying the effects of radiation injury to the lung. Since WR2721 does not totally protect against lung damage, it is reasonable to hypothesize

that different cellular compartments may be affected to varying degrees. This can only be detected by quantitative ultrastructural study. It also seems reasonable to hypothesize that, if WR2721 is more efficacious in preventing the late effects of radiation injury than the early effects, combined use of WR2721 with an agent (such as corticosteroids) which will reduce mortality in the early stages, should result in improved protection.

(3) Effect of corticosteroids on radiation injury to the lung

We are not aware of any controlled clinical trials in humans. However, in at least one noncontrolled study, prednisone administered soon after the onset of radiation pneumonitis was associated with a dramatic clinical response (22). The use of corticosteroids has been studied in rats and mice given thoracic irradiation and in several studies, significantly reduced the mortality as well as changes in lung compliance (5,6). In the study by Moss and associates (6), the changes in lung compliance observed in radiated control rats was almost completely absent in rats given cortisone continuously from the time of thoracic irradiation. The changes were also somewhat less in those given cortisone at the time of onset of radiation changes in the lungs, i.e. about 4 weeks after irradiation. Phillips and associates studied pulmonary lethality in irradiated mice (5); prednisolone was given from 7 days before to 60 days after irradiation and significantly reduced mortality. When prednisolone was given from 100 to 160 days after irradiation, i.e. during the time that most of the untreated mice died, it almost completely prevented deaths during the period of treatment. However, as soon as therapy was stopped, there were a large number of deaths. In one study where a lower dose of steroids was given and 3000 rads of radiation was administered as a single dose to one hemithorax, the mortality rate was not reduced (23). Corticosteroids have also been found to have some effect on early changes in surfactant after irradiation (7). Thus in summary, although there have been no morphological studies or controlled clinical trials, corticosteroids when administered early in the time period after irradiation seemed to prevent the development of radiation pneumonitis or the functional and lethal effects of it.

APPROACH TO PROBLEM

We will study each of 4 different experimental groups at 3 different time points; there will thus be 12 different sub-groups.

<u>Experimental Groups</u>	<u>Time Post-Radiation</u>		
	12 weeks	6 months	12 months
1. Controls	+	+	+
2. Radiated	+	+	+
3. WR2721 + Radiation	+	+	+
4. WR2721 + Radiation + Corticosteroids	+	+	+

In each sub-group, 3 different types of measurement will be performed:

- (a) Morphometry of the lung ultrastructure.
- (b) Measurement of lung elastic recoil.
- (c) Measurement of the pattern of ventilation.

A minimum of 8 animals will be studied for each measurement. Since (a) and (b) cannot be obtained in the same animal, different sets of animals will have to be studied to obtain both measurements.

RESULTS

Tables 1 and 2 enumerate the morphometric findings for the 4 different groups. Because of the long time required to perform ultrastructural morphometric analysis, the first groups of animals were all used for that purpose.

DISCUSSION OF RESULTS

At 12 weeks post-radiation, with morphometry partially or wholly completed on less than half the irradiated animals scheduled to be studied at this early timepoint, the WR2721 alone does not seem to confirm significant protection from radiation lung injury due to 3000 rads. It is possible that there may be less interstitial cell proliferation, but the numbers are not yet large enough for statistical significance.

On the other hand, the radiated animals that were treated with both WR2721 and corticosteroids had a number of significant differences from the group treated with radiation alone. Among these the ones probably most significant from the viewpoint of limitation of radiation injury were:

- (i) The total volume of cellular interstitium in the WR2721 + steroids group was less than half of that in the radiated group and not significantly different from controls.
- (ii) The total volume of non-cellular interstitium (extra-cellular matrix including collagen fibres) was only about 40% of that in radiated animals although the large variation in the radiated group prevented the changes from being statistically significant.
- (iii) The number of alveolar macrophages was less than 10% of that in the radiated group.
- (iv) The total volume of inter-capillary blood was almost double that in radiated animals (although still less than in controls); again, the relatively few animals and the high variability in the radiated group prevented the changes from reaching statistical significance.
- (v) The mean thickness of the interstitium in the WR2721 + steroid group was only about a third of that in the radiated group although again the changes were not statistically significant because of variability. Significantly, the mean value in the WR2721 + steroid group was very similar to that in the control animals.
- (vi) The total number of interstitial cells in the WR2721 + steroid group was only about 40% of that in the radiation group; this probably indicates less interstitial cell (including fibroblasts) proliferation. However, the number is also less than in the control group and may be related to the beneficial effect on fibroblast proliferation as well as the possibly detrimental effect of macrophage depletion.

Table 1 Changes in cell number and total volumes in the left lung of rats 12 weeks after unilateral irradiation. All data is mean \pm SEM.

No. of Cells Per Left Lung ($\times 10^6$)	Control Group				12 Weeks Post- Radiation+WR2721 +Corticosteroids	
	12 Weeks Post- Radiation		12 Weeks Post- Radiation+WR2721		12 Weeks Post- Radiation+WR2721 +Corticosteroids	
n	4	3	2	3	3	3
Type 1 epithelial cells	18.3 \pm 6.9	17.6 \pm 4.3	14.4 \pm 2.0	20.6 \pm 1.4	20.6 \pm 1.4	20.6 \pm 1.4
Type 2 epithelial cells	39.7 \pm 8.8 *	11.5 \pm 3.7	8.2 \pm 2.5	18.0 \pm 5.3	18.0 \pm 5.3	18.0 \pm 5.3
Interstitial cells	77.8 \pm 12.4	102.3 \pm 15.9	74.1 \pm 21.7	40.0 \pm 3.3 *	40.0 \pm 3.3 *	40.0 \pm 3.3 *
Capillary endothelial cells	128.0 \pm 11.0 *	41.8 \pm 9.3	49.7 \pm 1.3	43.5 \pm 3.9	43.5 \pm 3.9	43.5 \pm 3.9
Alveolar macrophages cells	9.9 \pm 4.0	9.7 \pm 3.2	10.1 \pm 2.8	3.7 \pm 0.8	3.7 \pm 0.8	3.7 \pm 0.8
Total Volume Per						
Left Lung (cm^3)						
n	4	4	4	4	4	4
Type 1 epithelial cells	.032 \pm .005	.037 \pm .007	.031 \pm .009	.019 \pm .002 *	.019 \pm .002 *	.019 \pm .002 *
Type 2 epithelial cells	.012 \pm .003	.019 \pm .007	.021 \pm .005	.014 \pm .002	.014 \pm .002	.014 \pm .002
Cellular interstitium	.034 \pm .006	.052 \pm .012	.052 \pm .007	.023 \pm .002	.023 \pm .002	.023 \pm .002
Non-cellular interstitium	.049 \pm .007	.090 \pm .036	.142 \pm .084	.037 \pm .003+	.037 \pm .003+	.037 \pm .003+
Capillary endothelial cells	.037 \pm .001	.032 \pm .011	.033 \pm .012	.021 \pm .001	.021 \pm .001	.021 \pm .001
Alveolar macrophages	.008 \pm .004 *	.024 \pm .007	.010 \pm .004	.002 \pm .001 *	.002 \pm .001 *	.002 \pm .001 *
Intracapillary blood	.214 \pm .010 *	.088 \pm .030	.137 \pm .066	.153 \pm .015 *	.153 \pm .015 *	.153 \pm .015 *
Intracapillary erythrocytes	.111 \pm .003 *	.044 \pm .017	.077 \pm .033	.083 \pm .010 *	.083 \pm .010 *	.083 \pm .010 *

* p < 0.05 vs radiation only group.

+ Important differences that are not statistically significant (see text).

Table 2 Changes in total surface area and mean arithmetic thickness in the left lung of rats 12 weeks after unilateral irradiation. All data is mean \pm SEM.

	n	Control Group	12 Weeks Post-Radiation	12 Weeks Post-Radiation+WR2721	12 Weeks Post-Radiation+WR2721+Corticosteroids
Total Surface Area Per Left Lung (cm ²)		4	4	4	4
Type 1 epithelium		1526 \pm 70	1225 \pm 393	1232 \pm 376	805 \pm 76
Type 2 epithelium		39 \pm 16	90 \pm 35	40 \pm 12	55 \pm 3
Capillary surface area		1433 \pm 84	1168 \pm 394	1131 \pm 424	864 \pm 133
Mean Thickness (μ)					
Epithelium		.278 \pm .016 *	.413 \pm .020	.427 \pm .061	.395 \pm .068
Interstitialium		.550 \pm .039 +	2.131 \pm 1.515	2.012 \pm .779	.725 \pm .130 +
Endothelium		.260 \pm .011	.269 \pm .023	.329 \pm .048	.247 \pm .022

* p < 0.05 vs radiation only group.

+ Important differences that are not statistically significant (see text).

In our original application and our previous reports, we had suggested that the protective effect of WR2721 might be more noticeable at the later timepoints and that steroids might help alleviate the early damage. Although the studies have not yet been completed on all the animals at 12 weeks post-radiation, our data suggest that this may be true.

OTHER ACCOMPLISHMENTS

(1) Irradiation of rats:

We have irradiated the following number of rats in each group:

Unilateral radiation	70 rats
Radiation + WR2721	70 rats
Radiation + WR2721 + steroids	46 rats

We have also had a total (sacrificed + current) of about 60 concurrent non-radiated controls.

(2) Post-irradiation duration:

Unilateral radiation:	10 rats sacrificed at 12 weeks
	8 rats sacrificed at 26 weeks
	8 rats now at 25 weeks
	30 rats now at 14-16 weeks
	10 rats now at 2 weeks
Radiation+WR2721:	10 rats sacrificed at 12 weeks
	8 rats sacrificed at 26 weeks
	8 rats now at 25 weeks
	30 rats now at 14-16 weeks
	10 rats now at 1-2 weeks
Radiation+WR2721+steroids:	8 rats sacrificed at 12 weeks
	8 rats at 20 weeks
	21 rats at 12-14 weeks
	6 rats at 1-2 weeks

(3) Processing of tissue:

Twenty-eight irradiated rats (12 weeks post-radiation) and 8 controls have had their lungs fixed and cubes of tissue randomly selected, dehydrated and embedded for electron microscopy. Six rats receiving radiation alone, 6 receiving radiation + WR2721, and 6 receiving corticosteroids + WR2721 + radiation have been thin-sectioned for electron microscopy and the sections have been stained.

(4) Morphometric measurements:

These have been described in Tables 1 and 2 on pages 2 and 3.

PROBLEMS ENCOUNTERED

(1) High mortality with bilateral irradiation

In our preliminary data submitted in the original proposal, we had studied rats 3 and 6 weeks after 3000 rads had been delivered bilaterally to both lungs. Although there was virtually no mortality at these timepoints, by 12 weeks after irradiation over 90% of the rats had died. This would have made the original protocol almost impossible to achieve logistically and the survivors would have represented a very biased sample. We tried reducing the dose of radiation delivered bilaterally from 3000 to 2500 rads. Again, the

survival after 12 weeks was very poor, only about 15%. After these failures, we began irradiating rats unilaterally with 3000 rads — which had the advantage of maintaining the original dose of radiation and which still allowed us to perform the proposed study. There was a 12-week post-radiation survival of over 90% in these rats. This was comparable to the 100% survival rate achieved with rats by Watanabe et al (20) and the 88% survival achieved with mice by Adamson et al (21) using 3000 rads delivered unilaterally to the lungs. Because our COTR, Colonel Davidson, was out of the country at the time, we addressed a formal request for change of protocol on March 8, 1983, to Dr. Howard Noyes in the Office of Research Management at WRAIR. Subsequently, we received permission from the US Army Medical Research and Development Command in Fort Detrick to proceed with the change in protocol. The new protocol has been effective and we will still be able to complete the proposed studies within the time and budget originally proposed.

(2) Problems with toxicity of WR2721

Initially, the batch of WR2721 received in 1981 was used in a dose of 500 mg/kg I.P. We found that 90% of the animals which received WR2721 + radiation died within 24 hours; this amounted to 12 rats. We, therefore, took the same batch of WR2721 and injected the same dose to non-irradiated rats. Again, all died. We requested a new batch of WR2721 and after telephone consultation with Captain Korte at Walter Reed, made the following changes:

- (a) Phosphate-buffered saline instead of saline was used as solvent.
- (b) The solution was made up at the last possible moment before injection.
- (c) Decreased the dose to 400 mg/kg I.P.

These changes plus perhaps the change in drug batch worked; no immediate deaths have subsequently occurred, although the rats receiving WR2721 still seem very subdued in comparison to saline-injected controls.

(3) Reduction of changes in breathing pattern following unilateral irradiation as opposed to bilateral irradiation

In some preliminary experiments with rats which were between 12 and 26 weeks post-unilateral irradiation, the changes in tidal volumes and rates were less than what had previously been seen after bilateral irradiation. This is very likely related to the fact that only 35% of the total lung volume is contributed by the left lung; therefore, the main mass of the normally functioning lung is unaffected by radiation even though radiation-induced injury and the protective effects of WR2721 and steroids, if any, in the left lung would still be representative of effects on lung tissue in general.

FUTURE PLANS

Having now obtained animals to initiate morphometric measurements (which are the most time-consuming part of the project) on all the different groups for the 12 and 26 post-radiation timepoints, we will proceed to irradiate animals for the physiologic studies. A major part of our effort will be to complete the morphometric studies on the 4 groups of animals 12 weeks post-irradiation and to begin studies on the 26 weeks post-irradiation animals. Although not part of the original proposal, we also have begun preliminary experiments on measurement of connective tissue components such as collagen and glycosaminoglycans which would be increased after radiation fibrosis.

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